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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,387	05/21/1999	ALAN SOLOMON	UNIE-014/01US 306680-2015	7724

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COOLEY GODWARD KRONISH LLP
ATTN: Patent Group
Suite 1100
777 - 6th Street, NW
WASHINGTON, DC 20001

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,387	SOLOMON ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,28 and 30-50* is/are pending in the application.

4a) Of the above claim(s) *28 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,30-35 and 37-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *24,28 and 30-50* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of U.S. Patent Application No. 09/316,387 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Gregory S. Emch, Technology Center 1600, Art Unit 1649.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 31 October 2007 has been entered.

Response to Amendment

Claim 50 has been added as requested in the amendment filed on 31 October 2007. Following the amendment, claims 24, 28 and 30-50 are pending in the instant application.

Claims 28 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper filed on 04 February 2002.

Claims 24, 30-35 and 37-50 are under examination in the instant office action.

Election/Restrictions

Applicants' arguments regarding non-elected claims 28 and 36 being rejoined with the elected claims currently under examination are acknowledged. The restriction/election requirement was made FINAL in the office action dated 09 May 2006 and was readdressed by the previous examiner in the office action dated 10 September 2007. As such, the merits of Applicants' arguments regarding the requirement will no longer be addressed. Applicants are reminded of their right to petition the requirement (see 37 CFR §1.144).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 24, 30, 31, 35, 39-46, 48 and 49 under 35 U.S.C. 102(b) as being anticipated by Konig et al. (WO 96/25435) is maintained for reasons of record and as set forth below.

In the response filed on 31 October 2007, Applicants argue that the Konig et al. does not teach each and every limitation of the claimed invention. Applicants also assert, "by showing that C-terminal antibodies, of which the monoclonal antibody disclosed by Konig 369.2B is a member, Applicants respectfully submit that they have

met their burden and provided a fact that the antibody of Konig does not necessarily opsonize and consequently fails to inherently anticipate the presently claimed invention." Applicants further assert that "Konig does not disclose a mechanism of action for opsonization, thus one of skill in the art would not have any direction to solve that problem." Finally, Applicants allege, "claims 30 to 33 are directed antibodies that are human, humanized, or chimeric. Konig does not state nor even contemplate that the antibodies disclosed in said reference can be human, humanized or chimeric. Thus, Konig does not anticipate claims 30 to 33."

Applicants' arguments have been fully considered and are not found persuasive. First, Applicants have not met their burden of showing that the Konig et al. reference is non-enabling. As previously noted, Applicants have provided no facts that the antibody of Konig fails to work via opsonization. Contrary to the comment that Applicants have met their burden and provided a fact that the antibody of Konig does not necessarily opsonize, this is indeed an assertion and not a fact. That Schenk notes that a specific C-terminal antibody 16C11 fails to affect amyloid plaque burden is irrelevant to the instant case, because it is a completely different antibody than the monoclonal 369.2B antibody disclosed by Konig. Schenk does not teach that any or all C-terminal antibody are ineffective. Thus, there is still no teaching in the art, nor any factual evidence brought forth on the record, that the 369.2B mAb would not be capable of removing amyloid deposits. That specific antibodies noted in other prior art fail to elicit the desired removal of amyloid would in fact call into question the enablement of the

broadly claimed current method, as the instant claims do not recite *any* specific antibody epitope and thus encompass *any* antibody or immunoglobulin polypeptide.

Regarding Applicants' comment that the Konig et al. reference does not disclose a mechanism for opsonization, the reference need not disclose such a mechanism. As previously noted, the mechanism of treatment is not required for Konig to be anticipatory or enabling, as it is inherent to the method steps taught by Konig. The reference teaches the use of specific antibodies in methods of treatment for Alzheimer's disease, wherein the treatment includes the extraction of β-amyloid species (see in particular p. 25, lines 14-18). The reference teaches the therapeutic administration of the antibodies in pharmaceutical formulations to Alzheimer's patients (see p. 7, lines 21-23, p. 14, lines 8-11, and p. 25, lines 14-18), which anticipates the method step of the claims. Moreover, Konig teaches that the 369.2B mAb binds to diffuse amyloid, fibrillar amyloid, vascular amyloid and neurofibrillary tangles (see p. 6, lines 23-25). It is noted at page 5, lines 1-3 of the instant specification that "[U]pon the binding or adhering of such immunoglobulin polypeptides to undesired deposits of amyloid fibrils, the latter are believed to be opsonized." And at page 12, lines 1-5, the instant specification defines "opsonize" as "the binding of an immunoglobulin polypeptide to a particular target, particularly epitopes found on deposits of amyloid fibrils, such that the antibody and targets together are recognized as "foreign" by the host's cellular immune system. In other words the binding of the immunoglobulin of the present invention enhances the phagocytization of the amyloid fibrils." Thus, as defined by Applicants' own disclosure, there would be no mechanistic difference between administration of the β-amyloid

specific monoclonal antibody disclosed by Konig and the instantly claimed antibodies, as the binding of these antibodies to amyloid fibrils would in both cases be expected to inherently enhance the opsonization of amyloid fibrils as mediated by the patient's own immune system. A prior art reference is not required to teach the mechanism of action in order to meet the requirements of either anticipation or enablement. As both Konig's therapeutic method and the currently claimed method provide for the administration of the same antibodies to the same patient population for the same purpose, the mechanism of removal of amyloid deposits would be inherently expected. Applicants are reminded that chemical compounds and their properties are inseparable (In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

With respect to Applicants' statement that Konig does contemplate that the antibodies can be human, humanized or chimeric and that thus, Konig does not anticipate claims 30 to 33, it is first noted that claims 32 and 33 are not a part of the instant rejection. Claim 30 requires a monoclonal antibody and claim 31 requires a human antibody. As first stated at p.6 of the office action dated 18 January 2001, the reference teaches "administration of monoclonal antibodies which bind amyloid fibrils, see in particular claims 9-20 and pp. 6-8 for treatment of Alzheimer's disease." As first stated at p.5 of the office action dated 30 September 2003, the reference teaches "the antibodies include human...see in particular p.22-24." Thus, the reference indeed anticipates claims 30 and 31. Therefore, the rejection of claims 24, 30, 31, 35, 39-46, 48 and 49 is maintained.

The rejection of claims 24, 30-35 and 37-49 under 35 U.S.C. 102(b) as being anticipated by Becker et al. (EP 613007) is maintained for reasons of record and as set forth below.

In the response filed on 31 October 2007, Applicants assert that the Becker et al. reference does not provide an enabling disclosure. Applicants assert that there was no effective animal model that could show that amyloid masses could be removed by an antibody *in vivo*. Thus, Applicants argue that the artisan would have to perform undue experimentation to practice the invention because the Becker et al. reference fails to provide any discussion of the effective amount of antibody that is to be administered to a patient to remove amyloid deposits *in vivo*. Applicants assert that the term "therapeutic" is not defined and that this may mean removing amyloid peptide from the body and not necessarily removing amyloid deposits. Applicants allege, "there are only *in vitro* examples in Becker, comparing neurotoxicity of β-amyloid *peptide* with and without β-sheet structure. There are no disclosure of any specific antibody, no antibody created, and no experiments with any antibody. Further, there are no *in vivo* data at all." Finally, Applicants assert that not all antibodies can opsonize a target and again cites the Schenk ('427) patent that describes the inability of the antibody 16C11 to remove amyloid deposits.

Applicants' arguments have been fully considered and are not found persuasive.

Contrary to Applicants' argument, there was an effective amyloid model to show that amyloid masses could be removed by an antibody *in vivo* (see for example, Kowall

et al. An in vivo model for the neurodegenerative effects of beta amyloid and protection by substance P. Proc Natl Acad Sci U S A. 1991 Aug 15;88(16):7247-51). Thus, given the *in vitro* guidance presented by the Becker et al. reference and the state of the prior art, it is well within the skill of the artisan to determine administrable amounts of the antibody sufficient to effect the desired response of binding to β-amyloid, inhibiting neurotoxicity and thus providing treatment. Further, the reference includes a definition of the term therapeutic. As noted previously, Becker specifically states that "therapeutics" means "treatment...of disease states or biological status via the *in vivo* administration to mammals, preferably humans, of the antibodies of the present invention" (column 7, lines 44-49; emphasis added). One of skill in the art would immediately recognize that such would mean administration of the antibody in an amount sufficient to elicit an effective (i.e., therapeutic) response. While the exact mechanism by which Becker's disclosed antibodies work to reduce neurotoxicity and thereby treat a patient having Alzheimer's disease may not have been fully appreciated by Becker, administration of the antibodies for therapeutic purposes would nonetheless inherently result in the opsonization of amyloid deposits as currently claimed. Regarding the Schenk patent, that Schenk notes that one specific C-terminal antibody 16C11 fails to affect amyloid plaque burden is irrelevant, because there are many other examples of antibodies that are effective (e.g., see the Konig et al. reference).

As stated previously, the question of anticipation here is whether or not the methods are the same or different. Applicants' claims are directed to a method of removing amyloid deposits in a patient comprising administering an antibody or

immunoglobulin polypeptide that opsonizes an amyloid fibril and induces removal of amyloid deposits. Alzheimer's disease is a neurodegenerative disorder characterized by the abnormal deposition of protein aggregates composed of neurofibrillary tangles and amyloid plaque cores (see Becker, column 1, lines 1-10). Becker also teaches that β-amyloid protein that adopts a β-sheet conformation (which conformation is known to form amyloid fibrils and subsequently aggregate into amyloid deposits) is particularly neurotoxic to neurons, and teaches that antibodies specific for β-amyloid peptides of the β-sheet conformation are useful for inhibiting the neurotoxicity of these peptides (see column 5, lines 27-50). Becker additionally teaches the therapeutic use of such antibodies for the treatment of human patients with Alzheimer's disease (column 7, 39-52). The instant claims evidence that the claimed antibodies are reactive with Alzheimer's Aβ protein (claim 41). Thus it can be seen that both Becker's therapeutic method and the currently claimed method provide for the administration of the same antibodies to the same patient population for the same purpose. Accordingly, the rejection of claims 24, 30-35 and 37-49 is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Konig et al (WO 96/25435).

The claim is directed to the method of claim 24, wherein maintenance doses are administered to the patient after removal of said amyloid deposits.

The Konig et al. reference teaches as set forth above, but does not explicitly teach administration of maintenance doses. However, the reference teaches that the

antibody disclosed therein provides for methods of preventing aggregation of β-amyloid and disrupting aggregation in Alzheimer's disease (p.13, lines 16-20). The reference also teaches that the antibody is useful for monitoring the level of β-amyloid peptide in the treatment of Alzheimer's disease (p.25, lines 13-17).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to provide maintenance doses as taught by the Konig et al. reference. This is because the reference teaches prevention of the disease, which encompasses patients, including those that have had amyloid deposits removed. Further, since the reference teaches monitoring the progression of the disease, it would have been obvious to assess the patient's status at a time after amyloid deposits have been removed and apply additional doses. The skilled artisan would have been motivated to make these modifications, since the reference teaches prevention and monitoring of the disease (p.13, lines 16-20; p.25, lines 13-17). The person of ordinary skill in the art would have had a reasonable expectation of success because the Konig et al. reference teaches that the methods would work (entire document).

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregory S. Emch/

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
29 January 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646